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Topic 20 – Electrophysiology, rythmology and pacing – E

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0211

Implications of baselines 2010 task force criterias on ventricular arrhythmias in ARVC

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Introduction: Arrythmogenic right ventricular cardiomyopathy (ARVC) is an autosomic dominant disease with a variable penetrance. Based on 2010 task force criteria, baselines characteristics of patients referred from 3 French centers were analyzed to identified risk factors for ventricular arrhythmias.

Methods: All patients with a diagnosis of ARVC referred from 3 academic French centers between 2006 and 2014 were included. The diagnosis was based on the 2010 Task Force. Occurrence of sustained ventricular arrhythmias and date of last alive status were collected from each center.

Results: The population consisted in 259 patients (171 males, sex ratio 1.9) with a mean age at diagnosis of 40+/-17 years. The VA group is composed of 61 patients (23.5%) who experienced at least 1.9 VT episodes. An ICD was implanted in 59% of them.

Mean follow-up was 4.0 years in "no VA group" and 7.5 years in "VA group" (p=0.0003).

Occurrence of syncope (OR=2.26, 95%CI [0.99-5.0], p=0.03) or VA (OR=3.1, 95%CI[1.8-5.2], p<0.0001) and sustained or non-sustained VA during exercise testing were associated (OR=4.2, 95%CI [0.90-19.5], p=0.03) with VA during follow-up. We failed to identify any ECG parameter related to the occurrence of VA.

Dilated right ventricular (RV) was significantly associated with VA during follow-up (OR = 3.6, 95%CI [1.36;9.65], p=0.005). Severe RV dysfunction was more often identified (10% vs 3%, p=0.06) in the "VA group" in echocardiography. By MRI, RVEF was significantly lower in "VA group" (34.6% vs 42.1%, p=0.03) but RV end diastolic volume and presence of akinesia or dyskinesia were not significantly different between two groups.

Genetic screening is on-going for all patients. Genetic screening will be performed using HaloPlex™ Target Enrichment System (Agilent Technologies) which allow the sequencing of 163 genes previously reported as involved in cardiac arrhythmias, conduction defect and cardiomyopathies**.**

Conclusion: Occurrence of syncope and VA at baseline or during exercise test are associated with occurrence of VA during follow-up. RV abnormalities on echocardiography and MRI are significantly associated with VT.

0417

SCN5A+/ΔQKP mice present late sodium current associated with long QT syndrome, dilated cardiomyopathy and ranolazine-sensitive spontaneous ventricular arrhythmias

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Deletion of QKP1507-1509 amino-acids in SCN5A gene product, the main cardiac Na+ channel Nav1.5, is associated with a large phenotypic spectrum of long QT syndrome (LQT3), dilated cardiomyopathy (DCM) and high incidence of youth sudden death. This mutation does not affect the peak Na+ current (INa) but rather increases the late/persistent Na+ current (INaL). In order to investigate the mechanisms implicated in the phenotype observed on the mutation carriers, a knock-in mouse model presenting the equivalent QKP1510-1512 mutation has been generated (Scn5a+/ΔQKP).

Mouse ECGs were recorded weekly from the age of 3 weeks. Na+ current was recorded with the whole cell patch-clamp technique in ventricular myocytes isolated from 4-week-old mice. Histological analysis was performed in paraffin sections of hearts of 4-week-old mice. At the age of 3 weeks, mice were treated with acute administration of ranolazine (30mg/kg i.p.) or β-blocker propranolol (0.3-1-3mg/kg i.p.) to suppress arrhythmias.

Scn5a+/ΔQKP mice in sinus rhythm displayed a prolonged QT interval (QTc = 64±2ms vs. 42±1ms in controls) with a high incidence of spontaneous ventricular extrasystoles and/or non-sustained tachycardia, leading to early mortality. Structural analysis showed right ventricular DCM. Voltage-dependent activation and inactivation properties were significantly altered in Scn5a+/ΔQKP mice, leading to an increase in the arrhythmogenic Na+ window current. INaL was enhanced by more than 2-fold in myocytes from Scn5a+/ΔQKP mice compared to control mice. At 3 weeks, ranolazine significantly decreased QTc and suppressed arrhythmias whereas propranolol alone had no beneficial effects.

Scn5a+/ΔQKP mice recapitulate a large part of the diverse clinical phenotype of patients carrying the equivalent mutation.

Our results show that the mutation induces a late Na+ current involved in the arrhythmogenic process. Ranolazine, rather than β-blockers, could be a good candidate for pharmacological treatment.

0441

Electrophysiological characterization of a novel SCN5A mutation causing Brugada syndrome, using cardiomyocytes differentiated from hiPSCs

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Rationale: Brugada syndrome is a human hereditary cardiac disease known to cause ventricular tachyarrhythmias (torsade de pointes) that can lead to sudden death. In about 20% of the Brugada affected patients, mutations have been identified in the gene encoding the Na+ ion channel, SCN5A. Up to now, genotype-phenotype studies have been performed using heterologous expression systems that lack the correct cellular context of a cardiomyocyte. Human Induced Pluripotent stem cells (hiPSCs) offer a now new paradigm for gene mutation characterization.

Objective: In this study, using cardiomyocytes differentiated from hiPSCs, we have electrophysiologically characterized a previously undescribed mutation in SCN5A gene, carried by a Brugada affected patient.

Methods and results: hiPSCs from a Brugada affected patient carrying the N1722D mutation in SCN5A have been generated and validated. hiPSCs from a healthy subject were used as control. Using patch clamp techniques, the biophysical properties of the Na+ channel and action potential characteristics were evaluated in both cardiomyocytes differentiated from these hiPSCs and in a mammalian expression system expressing the mutant channel. Preliminary data from both cellular models suggest a three-times reduction in Na+ current. The hiPSCs-derived cardiomyocytes revealed a specific action potential phenotype which is still under investigation.

Conclusion: Brugada syndrome modeling using hiPSCs-derived cardiomyocytes suggests that this cellular model recapitulates the characteristics of a loss-of-function Na+ channel mutation and that hiPSCs-derived cardiomyocytes can be used as an accurate model for cardiac Na+ channel disease.

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